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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,040	11/21/2006	Bin Wang	133232.00201	5612
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Pepper Hamilton LLP 400 Berwyn Park 899 Cassatt Road Berwyn, PA 19312-1183			EXAMINER GANGLE, BRIAN J	
			ART UNIT 1645	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/590,040	Applicant(s) WANG ET AL.	
	Examiner BRIAN J. GANGLE	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 October 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,9-12,20-37 is/are pending in the application.
- 4a) Of the above claim(s) 22-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 9-12 20 21 30-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 January 2009 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment and remarks, filed 10/5/2010, are acknowledged. New claims 36-37 are added. Claims 1, 9-12, and 20-37 are pending. Claims 22-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/27/2008. Claims 1, 9-12, 20, 21 and 30-35 are currently under examination.

The declaration of Bin Wang, under 37 CFR 1.132 filed 7/6/2010 is insufficient to overcome the rejection of claims 1, 9-12, 20-21, and 30-37 for reasons that will be discussed below in the rejection.

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 10-12, 20, 30-35, and newly submitted claims 36-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

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claims 1, 10, and 11 of copending Application No. 11/644,435, for the reasons set forth in the previous office action.

Applicant argues:

That the rejection should be withdrawn since all the other rejections have been obviated and this is the only remaining rejection.

Applicant's arguments have been fully considered and deemed non-persuasive.

According to MPEP 804:

Where this issue can be addressed without violating the confidential status of applications (35 U.S.C. 122), the courts have sanctioned the practice of making applicant aware of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the ground of double patenting. *In re Mott*, 539 F.2d 1291, 190 USPQ 536 (CCPA 1976); *In re Wetterau*, 356 F.2d 556, 148 USPQ 499 (CCPA 1966). The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.

The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.

Therefore, the rejection is proper and is maintained.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending Application No. 11/644,435 are drawn to a composition comprising a eukaryotic cell expression vector containing nucleotide sequences encoding an allergenic protein or a polypeptide that comprises an antigenic epitope of said allergenic protein and the protein or polypeptide that comprises an antigenic epitope of said protein. Said vector comprises an RSV, CMV, or SV40 promoter and the vector is in proportion to the protein in a ratio of 1:5 to 5:1. Though the copending claims do not recite inhibition of a Th1 T-cell immune response or a decrease in interferon- γ levels, they do recite identical structures. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9-12, 20-21, and 30-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the rejection of claims 1, 9-12, 20-21, and 30-35, as set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That the written description requirement is satisfied because the specification explicitly describes the claimed invention and provides a working example of the invention.
2. That the examiner's reference to antibody production induced by the claimed invention is irrelevant because the claims are drawn to inhibition of the Th1 response, which is a cellular response, not an antibody response. Applicant argues, that the analysis used by the office to determine whether the written description guidelines have been met is flawed because applicant has not claimed or asserted that the invention would alter the antibody response.
3. That Figure 11 of the application shows that the production of interferon- γ is decreased in the presence of the inhibitors of the presently claimed invention. Therefore, applicants were in possession of a composition for inhibiting a Th1 T-cell immune response.
4. That the invention satisfies the written description requirements because the specification provides structural characteristics that allow one of skill in the art to immediately envisage the claimed composition. Applicant asserts that claim 1 states that the composition comprises a nucleic acid eukaryote cell expression carrier encoding a targeted antigen; and the targeted antigen polypeptide that is encoded by said nucleic acid eukaryote cell expression carrier, where in the ratio of the nucleic acid eukaryote cell expression carrier to the antigen polypeptide is 5:1, from 2:1 to 10:1, from 1:5 to 5:1, or from 1:2 to 1:10. Applicant argues that the specification discloses the structural features of the claimed composition and that the written

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description requirement requires nothing more. Applicant argues that the written description rejection is tantamount to an enablement rejection which is analyzed under a different set of criteria.

5. That the “presently claimed specification describes more than just a function, it describe the structure of the presently claimed invention.” Applicant argues that since the compositions are described by a specific structure, one of skill in the art could immediately envisage the structure of the presently claimed composition and there is no requirement that every possible antigen that could be used be described, nor is there a requirement to provide working examples of every species. Applicant asserts that they have disclosed a sufficient number of species and described the common structural features of the presently claimed invention.

6. That the Federal Circuit, in *Ariad*, stated that the written description requirement does not demand either examples or an actual reduction to practice, but that instead, a constructive reduction to practice can satisfy the written description requirement. Applicant asserts that they have provided a constructive and actual reduction to practice that definitively identifies the claimed invention and shows that applicant was in possession of the invention.

7. That the Federal Circuit has overturned a rejection similar to the instant rejection in *Capon v. Eshhar*. Applicant asserts that the claims are rejected because they have not exemplified every composition with every possible antigen and argues that the Federal Circuit overturned the rejection in *Capon v. Eshhar* because there is no need to re-describe what is already known. Applicant argues that they are not required to list every possible antigen that could be used.

8. That the facts used by the office to support the rejection are wrong and that the office's assertion that the specification does not include working examples is inaccurate. Applicant argues that the specification includes a working example, thus the office's conclusion is wrong and the rejection is thus improper.

9. That the references cited by the office do not support a conclusion that the claims are not supported by sufficient written description. Applicant argues that the uncertainty the examiner alleges is not suitable for a written description rejection and then restates the above arguments that the working example shows that applicant was in possession of the invention and

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that there is sufficient description to allow one to envisage and recognize that applicant had possession.

10. That, in contrast to the facts in *Ariad*, the present specification provides examples of concrete and non-hypothetical compositions that are Th1 T-cell inhibitors that fall within the scope of the presently claimed invention. Applicant argues that this is unlike the case in *Ariad*; therefore, the claims meet the written description requirement.

Applicant's arguments have been fully considered and are not persuasive.

Regarding argument 1, applicant's claims are to a genus that covers a multitude of complex and poorly understood Th1 immune responses, as well as every antigen on earth, nucleic acids using a multitude of promoters, with any dosage of the inhibitor in any animal that has Th1 cells and with a ratio of nucleic acid to protein that ranges from 10:1 to 1:10. This is extraordinarily broad. Applicant's working example uses a single DNA construct with a single antigen at a single ratio and a single dosage and shows a decrease in only two of the many types of Th1 response (and, based on the discrepancy between the results shown in Figure 11 and what is stated in the specification, even this might not be the case).

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after

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only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.) On the other hand, there may be situations where one species adequately supports a genus. See, e.g., Rasmussen, 650 F.2d at 1214, 211 USPQ at 326-27 (disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered); In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."); In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant's invention includes the use of "inert fluid" broadly.).

The Federal Circuit has explained that a specification cannot always support expansive claim language and satisfy the requirements of 35 U.S.C. 112 "merely by clearly describing one embodiment of the thing claimed." LizardTech v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1346, 76 USPQ2d 1731, 1733 (Fed. Cir. 2005). The issue is whether a person skilled in the art would understand applicant to have invented, and been in possession of, the invention as broadly claimed. In LizardTech, claims to a generic method of making a seamless discrete wavelet

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transformation (DWT) were held invalid under 35 U.S.C. 112, first paragraph because the specification taught only one particular method for making a seamless DWT and there was no evidence that the specification contemplated a more generic method. See also *Tronzo v. Biomet*, 156 F.3d at 1159, 47 USPQ2d at 1833 (Fed. Cir. 1998), wherein the disclosure of a species in the parent application did not suffice to provide written description support for the genus in the child application.

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*.

The single example shows a decrease in interferon- γ levels. Applicant has not provided any reason why one of skill in the art would expect the single example to be representative of what is encompassed by the claims. In fact, since there are multiple examples in the art of compositions with the structural features of the invention that actually cause an increase in interferon- γ levels, one of skill in the art would not expect the single example shown to be representative of the rest of the genus.

Regarding argument 2, first, it should be clear, upon a fair reading of the rejections, that the analysis was not based solely on the specification's showing of antibody responses. This was only part of the reasoning, and in fact, only a small part. However, as would also be clear to one of skill in the art, antibody responses are indeed relevant to the instant case. Th1 cells are mainly responsible for cellular immunity against intracellular microorganisms. They affect IgG_{2a} antibody synthesis and antibody-dependent cell-mediated cytotoxicity. Intracellular microbial infections induce Th1 cell development which facilitates elimination of the microorganisms by phagocytosis. Th1 cells induce synthesis of antibody, which activates complement and serves as an opsonin that facilitates phagocytosis. Their main function is to induce phagocyte-mediated defense against infections. As such, one would expect, if Th1 responses were being inhibited, a

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decrease in antibody levels upon administration of the claimed invention. The specification showed no such decrease.

Regarding argument 3, applicant is correct that applicant was in possession of a composition for inhibiting a Th1 T-cell immune response. However, as discussed above, this is not representative of what is encompassed by the claims.

Regarding argument 4, applicant's description of the claimed invention leaves out a very important part of the claim. If the claim read as applicant asserts, there would not be a written description rejection over it; as one could indeed immediately envision the structures applicant asserts are in the claim. However, the claimed invention is not limited solely by structure. The claim also requires that the composition be effective to inhibit a Th1 T-cell immune response. The art clearly shows that simply combining a nucleic acid encoding an antigen and the antigen does not make for a composition that inhibits Th1 T-cell immune responses. Thus, while some of these compositions might inhibit a particular response, others clearly do not. Applicant has not described which structures are capable of the required function, nor described a correlation between the structure of the invention and the function required for the invention, and has provided no guidance that would lead one to such a correlation. Therefore, this is clearly a written description issue.

Regarding arguments 5 and 6, the claims are not limited solely by function or solely by structure. They contain partial structure and function. Therefore, there must be a disclosed correlation between this structure and the function. This is what is lacking from the specification. Applicant has not been asked to provide a working example for every species nor a description of every antigen. What is required is that a representative number of species be disclosed. As stated above, for inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*. When the evidence is weighed, it is clear that applicant's sole working example cannot be extrapolated to the multitude of species that are encompassed by the claims. Applicant's own data bears this out, as there was no inhibition of Th1 responses other than interferon- γ and IL-2, and, in the art, compositions with the same structural features have the opposite effect of applicant's exemplified embodiment.

Regarding argument 7, it should be made clear that the claims are not rejected because they have not exemplified every composition with every possible antigen. The claims are rejected because applicant has not described a correlation between the partial structure recited in the claims and the function recited in the claims. The claims encompass a huge and varied genus and those of skill in the art would not, based on the teachings of the art and the specification, expect the structure recited in the claims to provide the function recited in the claims. *Capon v. Eshhar* is wholly unrelated to the instant rejection. In *Capon v. Eshhar* the court vacated and remanded the case stating that the Board had erred in ruling that 35 USC 112 imposes a per se rule requiring recitation of known sequences. It is noteworthy that the court did not rule that the claims met the written description requirement; only that the Board did not properly consider the claims. This is unrelated to the instant case because applicant is not being asked to re-describe what is known. Despite applicant's assertion, they have not been asked to list every antigen that could be used in the invention. What is required is that applicant describe what structural features within the claims provide the function required by the claims.

Regarding argument 8, the specification contains one working example which uses a single DNA construct with a single antigen at a single ratio and a single dosage and shows a decrease in only certain types of Th1 response. For the reasons discussed above, this is not representative of the claimed genus. Other than this single example, applicant has not shown that any of the facts used in the rejection are incorrect.

Regarding argument 9, applicant's arguments with respect to the single example showing possession of the claimed genus have been dealt with above. With regard to the propriety of an analysis of uncertainty in written description rejections, the courts have found that unpredictability is relevant to the written description analysis. "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*.

Regarding argument 10, contrary to applicant's assertion, the specification does not provide examples of Th1 T-cell inhibitors. The specification provides a single composition that decreases interferon- γ and IL-2 production. This does not equate to any Th1 cell immune response, so applicant has provided a single working example that is hardly commensurate with the scope of the claims.

As outlined previously, the instant claims are drawn to compositions comprising a nucleic acid eukaryote cell expression carrier encoding a targeted antigen and the targeted antigen, wherein the ratio of carrier to polypeptide is 5:1, from 2:1 to 10:1, from 1:5 to 5:1, or from 1:2 to 1:10, and wherein the composition must inhibit a Th1 T-cell immune response. The claims encompass compositions comprising any antigen, not only from every pathogen in the world, but also from every organism in the world, including self antigens, tumor antigens, plant, protozoan, bacterial, and viral antigens.

The specification asserts that a composition comprising a protein antigen and the DNA that encodes it is a T-cell immune response inhibitor, specifically, a Th1 inhibitor. However, the specification contains only one example where inhibition of a Th1 T-cell response was shown. The specification discloses several examples where bovine foot and mouth disease virus (FMDV) antigen VP1 and an expression vector encoding VP1 were administered to mice, as well as various treatments such as VP1 protein alone, VP1 vector alone, whole virus vaccine alone, or VP1 protein followed by VP1 vector at 14 days or vice versa. The combination of protein and expression vector elicited the same level of antibodies as the other treatments. The combination of protein and expression vector led to T-cell expansion in every case. The level of T-cell expansion was less than that induced by either the protein or the vector alone, but T-cell expansion was shown. There were no tests performed that looked specifically at Th1 cells. There is one example that shows administration of a specific DNA construct at 100mg combined with 200mg of VP1 protein. This appears to decrease interferon- γ and IL-2.

The art does not provide any support for the notion that a protein antigen mixed with the DNA encoding it is a Th1 inhibitor. The idea of mixing antigens with the DNA encoding them is not novel and has been disclosed by several authors as a vaccine. Pundi et al. (WO 02/078732 A1, 10/2002) disclose a vaccine formulation comprising a DNA vaccine that encodes a polypeptide of a virus as well as the inactivated virus (see abstract). Wen et al. (US Patent

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6,221,664, 4/2001) disclose a vaccine comprising hepatitis B surface antigen as well as plasmid DNA which encodes said antigen and an adjuvant (see column 5, lines 1-26). In fact, in column 3, Wen states that interferon- γ was increased by administration of the composition. As interferon- γ is the signature cytokine of Th1 cells, it appears that the composition of Wen actually increases the Th1 response. Shrivastava et al. (Vaccine, 27:6582-6588, 2009) used hepatitis E or B antigens mixed with the DNA encoding them to immunize mice and found an increase in the Th1 response (see section 3.3.1 and page 6587, column 1, final paragraph and column 2, paragraph 2).

To meet the limitations of the claims, the compositions must inhibit a Th1 cell response. Inducing a lesser response than a standard vaccine is not inhibition; in fact it is the opposite of inhibition. The specification, the art, and applicant's arguments show that there is no correlation between the structural features of the claimed invention and the function of the claimed invention. Simply combining a protein antigen with DNA encoding it does not necessarily inhibit the Th1 response, and the specification provides no guidance as to what structures will have this function.

Claims 1, 9-12, 19-21, 30-35, and newly submitted claims 36-37, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues:

1. That the office has not articulated a reason to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Applicant asserts that the office has failed to provide any evidence to support its assertions and argues that the office's "unsubstantiated allegation that the claims are not enabled based on unsubstantiated claims of uncertainty" cannot be maintained.

2. That the specification provides a working example of a composition that is effective to inhibit a Th1 T-cell response. Applicant asserts that this example shows a composition that decreases interferon- γ , stating that this “demonstrates that the Th1 T-cell response is being inhibited.”

3. That the office’s observation that antibody levels are increased upon administration of the composition is irrelevant because the claims are not directed to a composition that is effective to inhibit an antibody response. Applicant argues that the composition is for inhibition of a Th1 T-cell response, which is not related to antibody production.

4. That the 132 declaration of Bin Wang shows that the claims are enabled because one of skill in the art can make and use the composition without undue experimentation. Applicant points to the declaration to show that compositions within the scope of the claims were used to inhibit a Th1 T-cell response for Flea antigen protein, zona pellucida 3 protein, insulin, Derp1 protein and OVA protein antigen. Applicant points out that the data includes data from a peer-reviewed publication and that the declaration states that Th1 T-cell immune response can be measured by measuring T cell proliferation.

Applicant’s arguments have been fully considered and are not persuasive.

Regarding argument 1, it is clear from reading the previous office action and from the rejection restated below, that applicant’s assertions are entirely incorrect. While applicant may disagree with the conclusions drawn by the examiner and with the reasoning set forth in the rejection, this does not mean that no evidence has been provided or that no reasoning has been articulated. Clearly both evidence and reasoning has been provided. Simply stating otherwise does not constitute argument or reasoning that will overcome the rejection.

Regarding argument 2, the specification provides only a single example of a composition that can decrease interferon- γ and IL-2. This is not commensurate with the scope of the claims. Interferon- γ and IL-2 are not “the Th1 T-cell response.” Th1 cells have many functions and are part of a very complex system. The phrase “a Th1 T-cell response” refers to many responses and interferon- γ and IL-2 production are a small portion of these. The fact that other measures of T-cell response were not inhibited by compositions that meet the structural requirements of the claims indicates that one cannot extrapolate the effects of a single composition on interferon- γ or

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IL-2 levels to the effects of a huge and varied genus of compositions on the multitude of responses that Th1 cells make.

Regarding argument 3, contrary to applicant's assertion, antibody responses are indeed relevant to the instant case. As those of skill in the art are aware, Th1 cells are mainly responsible for cellular immunity against intracellular microorganisms. They affect IgG_{2a} antibody synthesis and antibody-dependent cell-mediated cytotoxicity. Intracellular microbial infections induce Th1 cell development which facilitates elimination of the microorganisms by phagocytosis. Th1 cells induce synthesis of antibody, which activates complement and serves as an opsonin that facilitates phagocytosis. Their main function is to induce phagocyte-mediated defense against infections. As such, one would expect, if Th1 responses were being inhibited, a decrease in antibody levels upon administration of the claimed invention. The specification showed no such decrease.

It is important to note that the claims encompass all types of Th1 responses. The specification must, therefore, provide support for all types of Th1 responses. To provide evidence that the claimed compositions inhibit Th1 responses, there are several experiments in the specification. Antibody production was tested, T cell proliferation was tested, and levels of IL-2 and interferon- γ were tested. Each of these is a measure of Th1 T-cell response and each was tested using a composition that met the structural limitations of the claims. While IL-2 and interferon- γ were decreased, antibody production and T cell proliferation were increased. Therefore it is clear that simply providing a composition that meets the structural limitations of the claims does not provide one with a composition that meets the functional limitations of the claims. Attorney argument to the contrary does not overcome the evidence in the specification.

Regarding argument 4, applicant's declaration is noted. The points raised in the declaration will be addressed in order.

In paragraph 3, Dr. Wang states that he or those under his direction have made compositions according to the claims. This is noted. However, as discussed above, producing a composition that has the structural features of the claims does not mean one has produced a composition with the functional features of the claims, nor has applicant shown that compositions representative of the large genus have been produced or tested.

In paragraph 4, Dr. Wang states a Th1 T-cell immune response can be measured by measuring T cell proliferation. This is accepted. This is noteworthy because both the specification and the data in the declaration show an increase in T cell proliferation upon administration of compositions meeting the structural requirements of the claims.

In paragraph 5, Dr. Wang refers to Exhibit 1 and states that upon administration of Flea Antigen protein and a nucleic acid encoding the same to mice, T cell proliferation was found to be inhibited as compared to a positive control and compared to mice that were contacted with just the peptide or just the nucleic acid. This is not surprising and is in line with what is shown in the specification. It is not, however, indicative of inhibition of a Th1 response. To meet the limitations of the claims, the compositions must inhibit a Th1 cell response. Inducing a lesser response than a standard vaccine or a positive control that is designed to induce a response is not inhibition. In fact it is the opposite of inhibition. Applicant's data shows that administering the composition provoked a Th1 response. It provoked less of a response than other compositions, but it still provoked a response. To show inhibition of a Th1 response, applicant should be comparing the claimed composition to a saline control where no response was induced. If T cell proliferation were decreased compared to this, it would show inhibition. No such comparison was made. BSA was used as a control and, looking to Figure 1a, one can see that the claimed composition induced a higher proliferation response than BSA. In addition to the T cell proliferation results shown in exhibit 1, there are other pertinent facts to be found. On page 2003, column 1, Jin et al. state that in this study and in a previous study, there were no differences in expression levels of interferon- γ between the groups. This is the opposite of what applicant showed in their specification. Jin et al. even state that this suggests that "the therapeutic effect might not be associated with the Th1 and Th2 responses in cats."

In paragraph 6, Dr. Wang refers to Exhibit 2 and states that T cell proliferation was inhibited as compared to the controls in mice that were contacted with a composition comprising a zona pellucida 3 protein and a nucleic acid encoding the same at ratios of 2:1 and 4:1. The exhibit is limited to a single graph with no context, so one cannot determine what the negative control was. But, the composition at a ratio of 1:1 (which is encompassed by the claims) induced far higher T cell proliferation than the control, while 4:1 induced slightly higher proliferation (though within the margin of error). The 2:1 ratio induced slightly less, though still within the

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margin of error. This highlights the unpredictability of the results of administering the composition. Two compositions encompassed by the claims increased proliferation and one might have decreased it. This is not evidence of inhibition, as Dr. Wang suggests.

In paragraph 7, Dr. Wang refers to Exhibit 3 and states that T cell proliferation was inhibited in mice contacted with insulin and a nucleic acid encoding insulin where the ratio was 1:2 and that the data was not consistent at a ratio of 1:4. The lack of data for inconsistency again highlights the unpredictability of the composition. In addition, when one examines the data in Exhibit 3, one sees that, once again, the compositions encompassed by the claims, with ratios of 4:1, 2:1, 1:1, and 1:2 are all higher than the negative control. In fact, only 1:2 is even close, the rest are far higher than the control.

In paragraph 8, Dr. Wang refers to Exhibit 4 and states that T cell proliferation was inhibited in mice contacted with OVA protein antigen and a nucleic acid encoding the same, and that a ratio was found that could be used to inhibit T cell proliferation and inhibit asthma. When one examines this exhibit, one sees that the data again do not bear out the assertions. All of the ratios except 1:2 were higher (in some cases far higher) than the BSA control. As for inhibition of asthma, as asthma is generally an allergic response that is considered a Th2 response, this data does not appear to be relevant.

In paragraph 9, Dr. Wang refers to Exhibit 5 and states that T cell proliferation was inhibited in mice contacted with Derp1 protein and a nucleic acid encoding the same. As in the other exhibits, when one examines the data, all of the compositions increased T cell proliferation compared to the negative control.

As stated above, it seems that administration of the claimed compositions induces less of a Th1 response than administration of standard vaccines. However, this is not what the claims are drawn to. The claimed compositions must inhibit a Th1 response. This is not shown by showing less proliferation than with something designed to produce a high response. It would be shown by a decrease in proliferation compared to a negative control. To summarize the data in the specification and in the declaration:

<u>Source</u>	<u>Type of response</u>	<u>Results</u>
Specification	Antibody production	increased
Specification	T cell proliferation	increased

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Specification	IL-2 production	decreased
Specification	interferon- γ	decreased
Exhibit 1	interferon- γ	same
Exhibit 1	T cell proliferation	increased
Exhibit 2	T cell proliferation	increased or decrease, depending on ratio
Exhibit 3	T cell proliferation	increased
Exhibit 4	T cell proliferation	increased or the same, depending on ratio
Exhibit 5	T cell proliferation	increased

In addition to the above results, Exhibit 1 states that the Th1 response may not be involved and the previously cited art shows compositions with antigen and the nucleic acid encoding it that increased interferon- γ production. The data presented by applicant, supplemented by the teachings of the art, show quite clearly that simply providing a composition meeting the structural limitations of the claims does not provide one with a composition that meets the functional requirements of the claims. Neither the specification nor the art provide any indication of what structural features would give the required functional characteristics, and given the enormous breadth of the claims, it would require undue experimentation to determine this.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be

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enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to compositions comprising a nucleic acid eukaryote cell expression carrier encoding a targeted antigen and the targeted antigen, wherein the ratio of carrier is 5:1, from 2:1 to 10:1, from 1:5 to 5:1, or from 1:2 to 1:10, and wherein the composition must inhibit a Th1 T-cell immune response.

Breadth of the claims: The claims encompass compositions comprising any antigen, not only from every pathogen in the world, but also from every organism in the world, including self antigens, tumor antigens, plant, protozoan, bacterial, and viral antigens.

Guidance of the specification/The existence of working examples: The specification asserts that a composition comprising a protein antigen and the DNA that encodes it is a T-cell immune response inhibitor, specifically, a Th1 inhibitor. However, the specification does not disclose any example where inhibition of a Th1 T-cell response was shown. The specification discloses several examples where bovine foot and mouth disease virus (FMDV) antigen VP1 and an expression vector encoding VP1 were administered to mice, as well as various treatments such as VP1 protein alone, VP1 vector alone, whole virus vaccine alone, or VP1 protein followed by VP1 vector at 14 days or vice versa. The combination of protein and expression vector elicited the same level of antibodies as the other treatments. The combination of protein and expression vector led to T-cell expansion in every case. The level of T-cell expansion was less than that induced by either the protein or the vector alone, but T-cell expansion was shown. There were no tests performed that looked specifically at Th1 cells. There is one example that shows administration of a specific DNA construct at 100mg combined with 200mg of VP1 protein. This appears to decrease interferon- γ and IL-2.

State of the art: The art does not provide any support for the notion that a protein antigen mixed with the DNA encoding it is a Th1 inhibitor. The idea of mixing antigens with the DNA encoding them is not novel and has been disclosed by several authors as a vaccine. Pundi et al. (WO 02/078732 A1, 10/2002) disclose a vaccine formulation comprising a DNA vaccine that encodes a polypeptide of a virus as well as the inactivated virus (see abstract). Wen et al.

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(US Patent 6,221,664, 4/2001) disclose a vaccine comprising hepatitis B surface antigen as well as plasmid DNA which encodes said antigen and an adjuvant (see column 5, lines 1-26). In fact, in column 3, Wen states that interferon- γ was increased by administration of the composition. As interferon- γ is the signature cytokine of Th1 cells, it appears that the composition of Wen actually increases the Th1 response. Shrivastava et al. (Vaccine, 27:6582-6588, 2009) used hepatitis E or B antigens mixed with the DNA encoding them to immunize mice and found an increase in the Th1 response (see section 3.3.1 and page 6587, column 1, final paragraph and column 2, paragraph 2).

In addition to the teachings of the specification and the art, which show an increase in the Th1 response rather than inhibition of the Th1 response, applicant's own arguments show that the claims are not enabled. As discussed above, both Wen et al. and Pundi et al. disclose compositions that meet the structural limitations of the claims. However, applicant has argued the use of these references in art rejections stating that the compositions do not have the required Th1 inhibition activity.

To meet the limitations of the claims, the compositions must inhibit a Th1 cell response. Inducing a lesser response than a standard vaccine is not inhibition. The specification, the art, and applicant's arguments show that simply combining a protein antigen with DNA encoding it does not inhibit the Th1 response, and the specification provides no guidance on any composition that does so. Therefore, in view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Patricia Duffy can be reached on (571) 272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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